



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

120
In re application of:
Bhattacharjee, et al.

Serial No.: 08/886,044

Filing Date: June 30, 1997

For: VACCINE AGAINST GRAM-NEGATIVE BACTERIAL INFECTIONS

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Group Art Unit: 1645

Examiner: S. Devi

ADDITIONAL EVIDENCE SUBMITTED UNDER MPEP 1207

Mail Stop NON-FEE AMENDMENT Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

This communication is responsive to the Notice of Non-Compliance dated December 11, 2003, concerning the above-referenced patent application.

The examiner notes that certain articles were provided for the first time with Appellants' Brief, and must be submitted in a paper separate from the brief. She identifies these articles as Morrison 1994, Gibb *et al.* 1992, Munford 1980, and Rietschel 1992.

Appellants now separately forward these articles and relevant comments regarding these articles under MPEP 1207. The articles are appended to this response as Exhibit A. It is noted that MPEP 1207 does not preclude the articles from being discussed and submitted with the Brief. Therefore, no revision of the Brief is necessary.

Morrison *et al.* 1994, Gibb *et al.* 1992, Munford 1980, and Rietschel 1992, all were provided in rebuttal of points raised for the first time in the Final Office Action or later. Morrison *et al.* 1994 was provided to rebut the examiner's characterization of Greisman's review article as "incomplete and/or selective," in order to demonstrate that researchers other than Greisman were echoing Greisman's sentiments that antisera to the J5 chemotype "do not appear capable of providing broad-spectrum protection." More particularly, in an Advisory Action dated June 1, 2000, the examiner suggested that Dr. Greisman was a lone voice crying

in the wilderness -- that he "fail[ed] to cite and/or discuss a plethora of positive studies, published in the art prior to the filing of the instant application." There are others, however, who echo Greisman's sentiments on this subject. Like Greisman, a highly respected group in Switzerland led by Baumgartner and Glausner also has questioned the strength of the data presented in positive studies. An article by Baumgartner (1991), of record, reviews many unsuccessful clinical trials.¹ Of the few successful trials reviewed, "the protection could not be attributed to anti-J5 LPS, anti-Re LPS or anti-lipid A antibodies" (page 923). In 1991, Young *et al.* reported studies demonstrating that protective activity is mediated solely by IgM antibody, and that IgG antibody exhibits ***no protective activity***. IgM antibody is very short-lived and unsuitable for long-term protection via active immunization. This is yet another factor militating against an anti-endotoxin vaccine as presently claimed. And as recently as 1997, Zanetti and Glauser conclude that the "failure of these trials concluded three decades of research on anti-endotoxin approaches..."² And even an article on which Munford is a coauthor states that "proof that therapies specifically targeting endotoxins work in human septic shock is still lacking."³ So Greisman is not alone in his pessimistic views relating to prevention and treatment of sepsis.

The other articles, Gibb *et al.* 1992, Munford 1980 and Rietschel *et al.* 1992, all were provided as evidence of the microheterogeneity of the core of LPS. Lugowski (1996) had previously been cited by applicants in support of this point. However, the examiner objected, for the first time in the Advisory Action dated June 1, 2000, that Lugowski (1996) has a date after appellants' filing date. Yet Lugowski (1996) had been cited much earlier by appellants, in the response dated January 14, 1999. In that response, appellants argued that:

While there are highly conserved epitopes in the LPS core, it now is known that there exists a microheterogeneity in these epitopes. See, *e.g.*, Table 1 in the manuscript "Vaccines and Antibodies in the Prevention and Treatment of Sepsis" and Figure 11 of Lugowski (copies appended). In studies by Lugowski *et al.* (1996), in which core LPS from *E. coli* was used as a vaccine, there was no binding to *Klebsiella* (applicants' J5 LPS/OMP vaccine does bind to *Klebsiella*, see below). Moreover, there was little cross reaction between antiserum raised against the core LPS of J5 and other cores from *E. coli*, including the prototype core R3 to which J5 *E.*

¹ Attached to response submitted January 14, 1999.

² Attached to response submitted January 14, 1999.

³ Morrison *et al.*, *ASM News*, 60:479 (1994).

coli belongs! Thus, even within *E. coli*, there are significant differences between core epitopes.

The examiner had not previously raised Lugowski's date as a "defect." Indeed, the examiner herself cited several articles with post-filing publication dates in an action dated August 19, 1999, as showing "the state of the art." See, for example, Tomita *et al.* 1995 and Jachymek 1995. Submission of further, pre-filing date articles submitted to show the microheterogeneity of the LPS core were timely submitted when they accompanied appellants' Appeal Brief.

A first of these articles, Munford *et al.*, was published in 1980 in *J. Bacteriology* 144:630. The paper is entitled "Size heterogeneity of *Salmonella typhimurium* LPS in outer membranes and culture supernatant membrane fragments." Thus, even given Munford's later claims of homogeneity, he recognizes some heterogeneity. Another earlier article which mentions the heterogeneity of the core is Gibb *et al.*, *J. Infect. Dis.* 166:1051 (1992). Gibb *et al.* examined 180 clinical isolates and found that 123 had an R1 core, 14 had an R2 core, 18 had an R3 core and 25 (14%) had none of these core types. This clearly shows the present of at least four core regions, with different patterns of reactivity. In addition to these four core regions, there exists microheterogeneity within each of the core regions, as previously discussed. For example, DiPadova was published before appellants' priority date and teaches that "microheterogeneity in the core structure is due to nonstoichiometric substitutions with phosphate and ethanolamine groups."⁴ All of these differences lead to a wide variation in core conformation.

Finally, an article by Ernst Rietschel, a highly respected LPS chemist, reports data which suggest that it is the conformation of the LPS core, and not its linear structure, that is important in the interaction of LPS with mammalian hosts. In other words, even if cores possess only limited heterogeneity they may interact differently in the host, since even limited heterogeneity can give rise to differences in folding, and hence, conformation. Rietschel's theory supports appellants' hypothesis, *infra*, that the OMP serves to present an important conformational epitope.

Appellants reiterate that submission and reliance on those articles which were not submitted until after Final Rejection under 37 CFR §1.116 is proper, since each of them was

⁴ DiPadova at page 3863, bottom of right-hand column. DiPadova was submitted with the response dated January 14, 1999.

used in rebuttal of a point first raised in the Final Rejection, which point was not necessitated by any amendment made by appellants. Accordingly, their entry into the record for Appeal is proper.

Respectfully submitted,

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Stephen A. Bent
Reg. No. 29,768

FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109
Telephone: (202) 672-5404
Facsimile: (202) 672-5399